Clinical Management of Gastrointestinal Stromal Tumors: Before and After STI-571

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Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. Until recently, surgery has been the only effective therapy for GIST. However, even after complete resection of tumor, many patients still eventually die of disease recurrence. Conventional chemotherapy and radiation therapy have been of limited value. Within the last few years, it was discovered that most GISTs have a gain-of-function mutation in the c-kit proto-oncogene. This results in ligand-independent activation of the KIT receptor tyrosine kinase and an unopposed stimulus for cell growth. STI-571 is a small molecule that selectively inhibits the enzymatic activity of the ABL, platelet-derived growth factor receptor, and KIT tyrosine kinases and the BCR-ABL fusion protein and is a landmark development in cancer therapy. Its clinical development marks a new era of rational and targeted molecular inhibition of cancer that emanates from direct collaborations between scientists and clinicians. It provides proof of the principle that a specific molecular inhibitor can drastically and selectively alter the survival of a neoplastic cell with a particular genetic aberration. The advent of STI-571 has markedly altered the clinical approach to GIST. It has proven to be effective in metastatic GIST and is also under investigation as a neoadjuvant and adjuvant therapy. HUM PATHOL 33:466-477. Copyright 2002, Elsevier Science (USA). All rights reserved.

Key words: gastrointestinal stromal tumor, sarcoma, STI-571, c-kit proto-oncogene, therapy, chemotherapy, surgery, radiation.

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ASCO, American Society of Clinical Oncology; ATP, adenosine triphosphate; CML, chronic myelogenous leukemia; EORTC, European Organization for Research and Treatment of Cancer; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma; MDACC, M.D. Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; PDGFR, platelet-derived growth factor receptor; PET, positron emission tomography.

Gastrointestinal stromal tumor (GIST), the most common mesenchymal tumor of the gastrointestinal (GI) tract, is thought to originate from the interstitial cell of Cajal, an intestinal pacemaker cell.[1] Clinically and pathologically, GIST represents a spectrum of tumors that include benign and malignant variants. The subset of GISTs that have a high likelihood of malignant behavior are generally identified by increased mitotic activity and larger tumor size. However, the prediction of malignant potential may be difficult; small tumors with low mitotic activity may still metastasize. Anatomic location is also important; a small GIST from the small intestine may have a worse prognosis than a large tumor from the stomach. GIST's immunophenotypic and genetic profiles clearly distinguish it from other mesenchymal tumors of the GI tract. GIST was previously classified as visceral leiomyosarcoma because of these 2 tumors' similar histologic appearance. Consequently, much of the older published data is of limited value because it includes a mixture of GIST and other intra-abdominal sarcomas. On immunohistochemistry, in contrast to true smooth-muscle tumors, GISTs are usually positive for expression of the KIT receptor tyrosine kinase (detected as CD117 antigen) and CD34, variably positive for smooth-muscle actin, and usually negative for desmin.[2,3] Unlike schwannomas, GISTs are usually negative for S100 protein. Although GIST has been recognized as a distinct tumor entity for about 10 years, only within the last few years has it been diagnosed with precision. This increased diagnostic precision has resulted from increasing awareness of GIST's existence and the widespread application of CD117 immunohistochemistry in the routine pathologic analysis of spindle and epithelioid neoplasms of the GI tract and associated anatomic regions.

In 1998, Hirota and colleagues reported that some GISTs contain an exon 11 mutation in the c-kit proto-oncogene that encodes KIT.[4] Normally, the ligand for KIT (the cytokine known as stem cell factor, Steel factor, or KIT ligand) binds and induces receptor dimerization, which facilitates increased kinase activity and autophosphorylation of tyrosine residues in the KIT homodimeric structure. These phosphorylated tyrosine residues serve as "docking" sites for adapter molecules and other proteins that are downstream substrates of KIT, including phosphatidylinositol 3-kinase. Phosphorylation of these effector molecules triggers a cascade of intracellular signals that stimulate proliferation and/or enhanced cellular survival. The presence of a gain-of-function c-kit mutation provides a constitutive stimulus for tumor cell growth and an uncontrolled antiapoptotic signal that favors the malignant clone. The prevalence of c-kit mutation in GIST is as high as 90%.[5,6]

The development of STI-571 (Imatinib [Gleevec]; Novartis, Basel, Switzerland) has revolutionized the treatment of GIST. This agent selectively inhibits the ABL, BCR-ABL, KIT, and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. STI-571 is a targeted therapy directed against the apparent fundamental and critical pathogenetic defect in GIST. The documented clinical efficacy of this agent provides proof that a specific inhibitor can drastically and selectively alter the survival of a neoplastic cell. The treatment of patients with GIST now requires a multidisciplinary team that includes medical oncologists, surgeons, and molecular and surgical pathologists.

This review outlines the clinical management and therapy of GIST, covering both the traditional approach and the use of STI-571. The review is based on presentations made at a 2001 National Institutes of Health Workshop on GIST, as well as on other data presented recently at research meetings, including the May 2001 Plenary Session of the American Society of Clinical Oncology.[6,7]

BEFORE STI-571

Primary Disease

The exact incidence of GIST in the United States is unknown at this time, because until very recently many of these cases were considered benign neoplasms or leiomyosarcoma. However, the estimated incidence of GIST is at least 1,000 new cases per year, and the actual incidence is probably much higher if very small (<1 cm) lesions found incidentally during laparotomy for other reasons are included. The awareness of GIST has increased because of the routine use of CD117 immunohistochemical staining in the pathologic analysis of tumors in which GIST is in the differential diagnosis. GISTs arise most commonly in the stomach, followed by the small intestine and then the colon, rectum, or esophagus. Occasionally, GIST originates outside the intestinal tract in the omentum, mesentery, or retroperitoneum. The age range at diagnosis is generally 40 to 80 (median, 58), and the incidence is slightly higher in men than in women.[8] The clinical presentation of GIST is variable. Often the tumor is "silent" until it reaches a large size, at which point it may cause nonspecific abdominal pain or discomfort or become recognized as a palpable mass. Up to 25% of patients present with acute hemorrhage into the intestinal tract or peritoneal cavity from tumor rupture.

Surgery

Surgical resection has been the mainstay of therapy for GIST. The primary goal of surgery is complete resection of disease with avoidance of tumor rupture. Unlike intestinal adenocarcinoma, GIST rarely metastasizes to lymph nodes, and thus lymphadenectomy is seldom warranted. Achieving negative pathologic margins of resection generally is not difficult because GIST tends to hang from, not diffusely infiltrate, the organ of origin. Consequently, wedge resection of the stomach or segmental resection of the intestine provides adequate therapy, and wide resection has no known benefit.[9]

The results of surgical therapy for primary GIST are confounded by the fact that most investigators have tended to lump together patients with primary and recurrent disease. This is because GIST is uncommon, and thus most single institutions have limited experience with it. These methodologic deficiencies obscure the actual results of resection and the relationship of pathologic markers to survival. In a recent analysis of 200 patients with GIST treated and followed prospectively at the Memorial Sloan-Kettering Cancer Center (MSKCC), 80 patients with primary tumor without metastasis underwent complete gross surgical resection, and their 5-year disease-specific survival rate was 54%.[8] On multivariate analysis of this patient subset, tumor size was an independent prognostic factor in survival (Fig 1); patients with tumors >10 cm had a disease-specific 5-year survival of only 20% after resection. Investigators at the M.D. Anderson Cancer Center (MDACC) have reported similar results.[10]

Tumor rupture before or during resection is another predictor of poor outcome.[10] Meticulous surgical dissection is imperative to avoid tumor rupture and intraperitoneal dissemination during the resection of these often soft and fragile tumors. A number of other pathologic features have also been correlated with survival, including mitotic index, aneuploidy, cellular morphometry, proliferative index, and percent S-phase fraction.[11]

Adjuvant Therapy

The standard of care after complete resection of a primary tumor has been observation. This in part reflects the inadequacy of conventional chemotherapeutic drugs for metastatic disease. Patients with a ruptured tumor or multifocal peritoneal nodules at the time of resection of the primary tumor have been treated with adjuvant therapy without demonstrable benefit. Although radiotherapy is essential in local therapy of extremity soft tissue sarcoma, its role in primary GIST is minimal.[12,13] Radiation is limited by its potential toxicity to surrounding structures, especially the intestine. It may have a role in positive microscopic margins in gastric or rectal GIST. Only anecdotal and case reports on the use of radiation in small numbers of patients have been published. One group reported adjuvant radiation (5040 cGy) after resection of a high-risk GIST.[14] Shioyama et al[15] reported a case of a retroperitoneal GIST treated with primary radiotherapy (5100 cGy), arterial chemotherapy, and immunotherapy (OK432). Serum lactic dehydrogenase levels normalized by the end of radiation therapy, with no change in tumor size noted on computed tomography (CT). Six years later, CT revealed a marked decrease in tumor size. Crosby et al[16] reported the use of postoperative radiotherapy in 10 patients with metastatic GIST originating from the small intestine. In 6 of 9 patients evaluated, the disease was "controlled" in the irradiated
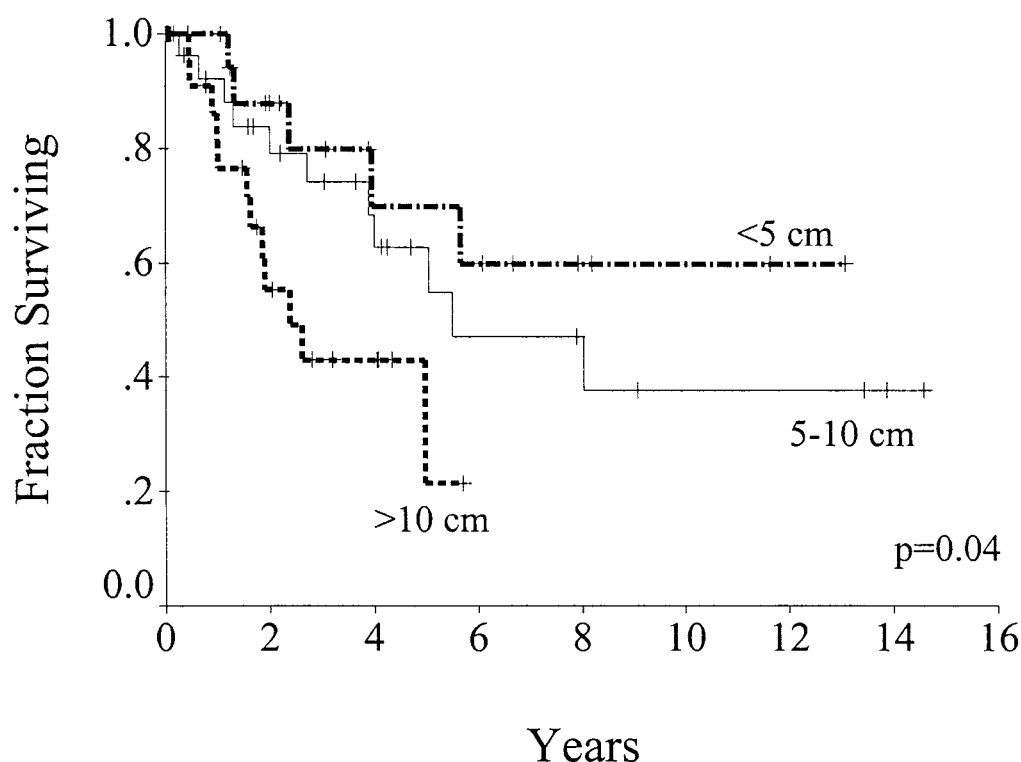
FIGURE 1. Disease-specific survival after complete resection of primary GIST based on tumor size. Eighty patients underwent complete gross resection of a primary GIST. Patients with tumors>10 cm (n = 27) had significantly worse survival than those with tumors between 5 and 10 cm (n = 30) or <5 cm (n = 23). Reproduced with permission.[8]

field, although the duration of response was not reported.

Metastatic Disease

Many patients develop recurrent GIST despite complete surgical resection of their primary tumor. In some cases this can be attributed to tumor rupture. However, recurrence may also follow what is ostensibly a curative resection, as a result of unsuspected microscopic tumor dissemination. At MDACC, only 10% of patients were disease free after extended follow-up.[10] The pattern of initial recurrence predominantly involves the peritoneal surface and/or the liver. In the MSKCC study, at a median follow-up of 24 months, 32 of the 80 patients (40%) who presented with primary disease and underwent complete gross resection developed recurrent disease. The site of first recurrence could be evaluated in 27 patients; the peritoneum was involved in about half of the cases and the liver in nearly two-thirds. At MDACC, 60% of 122 patients recurred within 2 years of primary tumor resection.[17] About 40% of these patients had isolated peritoneal disease. Unfortunately, after resection of recurrent GIST, the median survival is only 15 months.[18] Until recently, treatment options for recurrent disease have been limited and included systemic or intraperitoneal chemotherapy, surgery, arterial embolization, and radiation.

Systemic Chemotherapy

It is difficult to accurately determine the response rate of GIST to conventional chemotherapeutic agents, but it appears to be extremely low (<10%). Because GIST has been routinely distinguished from intra-abdominal leiomyosarcoma (LMS) only recently, interpretation of most chemotherapy trials of intra-abdominal soft tissue sarcoma is problematic, if not impossible.[19] Assuming that most tumors classified previously as "gastrointestinal LMS" were actually GIST, the response rate of GIST from older chemotherapy trials can be estimated. Analysis of these published trials reveals the partial response rate to a variety of agents to be minimal (0 to 15%) (Table 1). Few published series have distinguished GIST from LMS prospectively. Investigators at the Mayo Clinic reported a phase II trial of dacarbazine, mitomycin C, doxorubicin, cisplatin, and growth factor support for patients with advanced GIST or LMS.[20] The objective response rate for patients with LMS was 67% (95% confidence interval [CI], 44 to 90), including a 33% response rate in those with "somatic" tumors. In contrast, only a partial single response was seen in the 21 patients with GIST, yielding an overall response rate of 4.8% (95% CI, 0 to 14.5). Similar results have been reported by investigators at the Dana Farber Cancer Institute for several chemotherapy regimens that have been tested for GIST.[21]

Based on the disappointing results with conventional agents, it has been difficult to recommend any particular agent or combination of drugs as standard care for metastatic GIST. The resistance of GIST to chemotherapy may relate to increased levels of P-glycoprotein and multidrug resistance protein compared to those found with LMS.[22] Alternatively, oncogenic activation of KIT in the vast majority of GIST may contribute to resistance through increased antiapoptotic sig-

TABLE 1. Response Rates to Chemotherapy in Patients With Metastatic GIST

Regimen	n	Partial Response n (%)	Reference
DOX + DTIC	43	3 (7%)	56
DOX + DTIC +/− IF	60	10 (15%)	57
DOX + DTIC+ IF	11	3 (27%)	58
IF + VP-16	10	0 (0%)	59
Paclitaxel	15	1 (7%)	60
Gemcitabine	17	0 (0%)	61
Liposomal DOX	15	0 (0%)	62
DOX	12	0 (0%)	62
DOX or docetaxel	9	0 (0%)	63
High-dose IF	26	NR (0–8%)	64
EPI + IF	13	0 (0%)	61,65
Various (e.g., DOX, gemcitabine, CT2584)	40	4 (10%)	21
DTIC + MMC + DOX + CDDP + GM−CSF	21	1 (5%)	20
TOTAL	266	22 (8.3%)	

Abbreviations: DOX, doxorubin; DTIC, dacarbazine; IF, ifosfamide; CDDP, cisplatin; VP16, etoposide; EPI, epirubicin; NR, not reported.

naling and/or activation of other drug resistance mechanisms.[5,23,24]

Surgery for Isolated Peritoneal Recurrence

Recurrence of GIST isolated to the peritoneal cavity may sometimes be treated with surgical resection. These peritoneal tumors tend to "sit" on the intestine, mesentery, omentum, or undersurface of the abdominal wall. They may be either near the site of the primary tumor or at a distant location and usually do not invade underlying organs and do not involve lymph nodes. Peritoneal recurrences of GIST can usually be removed with limited resection. Cross-sectional imaging often does not accurately represent the extent of peritoneal disease, and the discovery of countless subcentimeter nodules at laparotomy is not unusual. Essentially all patients with peritoneal disease will develop subsequent recurrence regardless of whether all gross tumor can be removed.

Intraperitoneal Chemotherapy

In an attempt to improve the results of surgical resection of peritoneal recurrence from GIST and other sarcomas, Sugarbaker et al[25] developed the strategy of cytoreduction and adjuvant intraperitoneal chemotherapy with cisplatin and doxorubicin. Eilber at UCLA extended this work using intraperitoneal mitoxantrone.[26,27] Topical therapy is attractive for recurrent peritoneal GIST because the tumors tend to superficial. Mitoxantrone, a derivative of doxorubicin, was chosen because it binds rapidly to intraperitoneal tissues and produces high local drug concentrations. Because systemic absorption is minimal, there is less toxicity than with intravenous administration. The combination of surgical resection or debulking and intraperitoneal mitoxantrone was shown to be both technically feasible and safe. Toxicity was infrequent and due primarily to inflammation, which resulted in bowel obstruction. In the presence of hepatic metastases, resection of peritoneal disease and intraperitoneal chemotherapy did not alter overall survival. However, in 27 patients with disease isolated to the peritoneum, the median time to recurrence was increased from 8 months to 21 months with the addition of intraperitoneal mitoxantrone. Therefore, this approach might conceivably provide benefit for patients with disease confined to the peritoneum. Intraperitoneal chemotherapy for recurrent GIST is now also being tested at MSKCC and MDACC, although it is currently reserved for patients with STI-571–resistant tumors.

Hepatic Artery Embolization of Liver Metastases

Hepatic artery embolization or chemoembolization is an attractive palliative option for patients with liver metastases from GIST. Arterial occlusion is effective in liver metastases from GIST because the tumors are typically hypervascular. Embolization may be repeated several times. Chemoembolization has several theoretical advantages over systemic chemotherapy, including mechanical occlusion of the arterial blood supply to the tumor, increased delivery of drug to the tumor, prolonged tumor exposure to the drug, and minimal systemic toxicity because of high first-pass hepatic clearance of the drug.[28] In an initial study, 14 patients with GIST metastatic to the liver were treated with hepatic infusion of polyvinyl alcohol sponge particles mixed with cisplatin powder, followed by intra-arterial delivery of vinblastine.[29] Ten patients (70%) had a partial response lasting from 8 to more than 31 months (median, 12 months) after an average of 2 embolizations. Toxicity included right upper quadrant pain, elevated hepatic enzyme levels, ileus, and mild myelosuppression. In this small series, the response rate of embolized lesions was vastly superior to the results of systemic chemotherapy. In a second, recent report of chemoembolization of liver metastases from GIST,[28] 11 patients with metastatic GIST underwent chemoembolization with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol particles 1 to 5 times at approximately monthly intervals. The partial response rate (total of 16 patients with liver metastases from sarcoma, 11 of whom had GIST) was 13%. Stable disease status was achieved in an additional 69% of patients. The median time to progression was 8 months. Postembolization syndrome was common, but no deaths occurred in the first 30 days after embolization.

It is not clear whether the results of chemoembolization are due to improved local delivery of chemotherapy or to the interruption of arterial blood supply. It should be noted that some investigators routinely use embolization of particles (e.g., polyvinyl alcohol particles) alone without chemotherapy and achieve comparable results (K.Brown and R.P. DeMatteo, unpublished data). Recall that no chemotherapeutic agent has been reported to have any substantial activity against GIST when administered systemically. Selective

arterial embolization also can be used to control bleeding from intrahepatic metastases.

Surgery of Liver Metastases

The liver is a common site of GIST recurrence. Most patients with liver metastases from GIST are unresectable due to diffuse intrahepatic disease or are inoperable due to extrahepatic disease. In a recent analysis of 331 patients with sarcoma metastatic to liver,[30] of 131 patients with GIST or "intestinal leiomyosarcoma," 34 underwent hepatic resection of all gross disease. The 1- and 3-year survival rates were 90% and 58%, respectively (Fig 2). The time interval from treatment of the primary tumor to the development of liver metastasis was a significant predictor of survival. The 5 patients who developed liver metastases at least 2 years after resection of their primary tumor each survived longer than 4 years after hepatectomy.

Radiation Therapy

Radiation therapy has only an occasional role in the management of metastatic GIST. It can be used to palliate patients with bleeding from peritoneal recurrence if the responsible tumor can be identified. Radiation is also useful to alleviate pain from a bulky liver metastasis or a tumor fixed in the pelvis or to the abdominal wall. Otherwise, the pattern of recurrence in the liver or the peritoneum is generally too diffuse to be amenable to radiation.

AFTER STI-571

Development of STI-571

The application of STI-571 represents a major paradigm shift in cancer therapy—targeting the specific molecular abnormalities crucial in the etiology of cancer. In contrast, most anticancer therapies developed over the past 50 years have been essentially nonspecific. Cytotoxic agents generally function by interfering with cell machinery common to both neoplastic and normal cells (e.g., DNA synthesis). Consequently, conventional chemotherapeutic agents lack selectivity, have a narrow therapeutic index, and generally induce toxicity. Much of the biotechnology-derived translational research of the late 1980s and 1990s focused on improving supportive care for patients undergoing chemotherapy. Growth factors, such as G-CSF and erythropoietin, were implemented to counteract the toxic impact of chemotherapy on hematopoiesis. However, because conventional chemotherapy remained ineffective against GIST even with the advent of growth factors, improved and more rationally directed approaches to GIST management were desperately needed.

A shift in the cancer therapy paradigm evolved in the late 1990s. The seeds of change were planted in the molecular insights gained from cancer research in a variety of fields, ranging from basic investigation in oncogene mechanisms of neoplastic transformation to the characterization of specific chromosomal defects in leukemias. It was known that certain leukemias harbored specific chromosomal aberrations, such as the
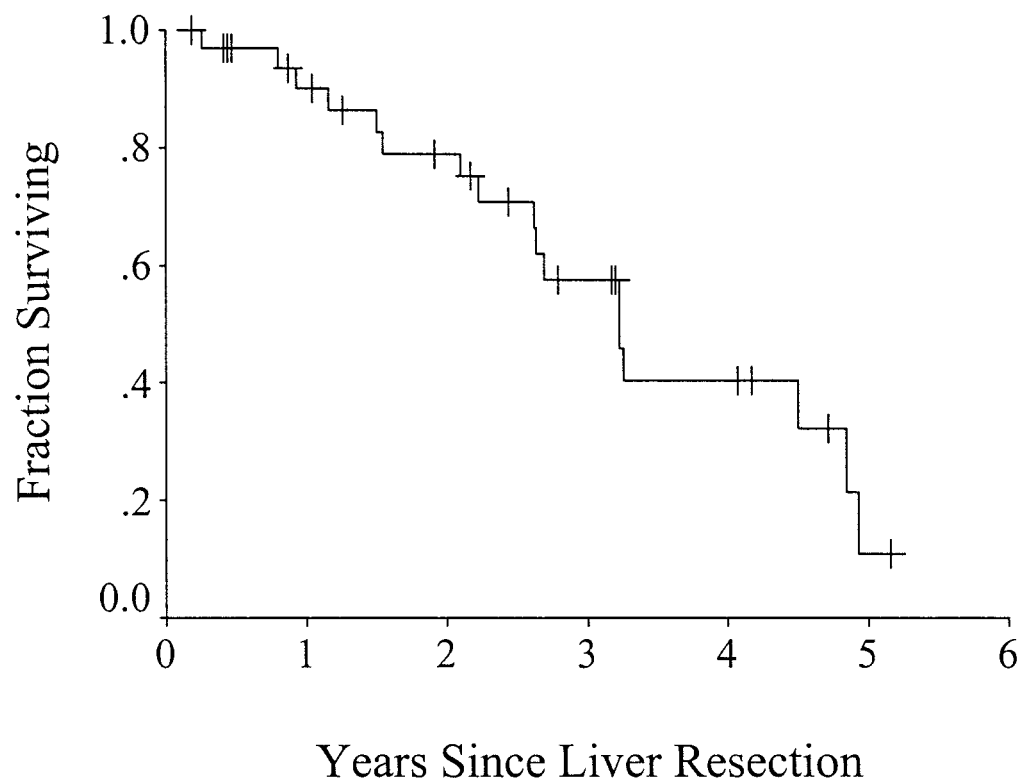

FIGURE 2. Disease-specific survival after complete resection on liver metastases from GIST. The median survival after hepatectomy was 3.2 years. Adapted with permission.[30]

balanced chromosome 9 and 22 translocation, giving rise to a new chimeric fusion protein in chronic myeloid leukemia (CML). This fusion protein, BCR-ABL, is known to have uncontrolled tyrosine kinase activity. It was postulated that this leads to constitutive intracellular signaling and induces the development of CML. Although data were available to support this hypothesis, considerable philosophic and logistical barriers impeded the development of an agent to inhibit BCR-ABL. First, it was believed that blocking BCR-ABL would produce overwhelming side effects. Many scientists postulated that competitive ATP inhibitors could never be selective to cancer cells, because the ATP binding pocket of most kinases is highly conserved. Thus, inhibition of 1 kinase would lead to inhibition of most, if not all, intracellular kinases, with potentially lethal consequences. Another philosophic problem that limited drug development was that CML is an uncommon disease and thus may not represent a sound economic investment. Nevertheless, Brian Druker at the Oregon Cancer Institute and scientists at the Swiss pharmaceutical company Novartis, including Nick Lydon, Alex Matter, Elisabeth Buchdunger, and many others, overcame these barriers. They identified the important activity of a small molecule, now known as STI-571, that could selectively block the ABL kinase activity and kill CML cells in vitro.[31] The translation of this finding into clinical trials has been remarkably rapid and dramatic. The preclinical paper by Druker was published in 1996, and the preliminary human data was presented at the Plenary Session of the American Society of Hematology in December 1999. Data from clinical trials in CML were published in early 2001.[32,33] Shortly thereafter, in May 2001, the U.S. Food and Drug Administration acknowledged the breakthrough by approving STI-571 as a safe and effective therapy for CML patients. STI-571's clinical efficacy has been striking, with greater than a 90% complete response rate in chronic-phase CML. The rapid clinical application of STI-571 for CML was supported by the strength of the science underpinning the mechanism of action of this novel agent.

Application of STI-571 to GIST

In 1998, Hirota et al[4] published their observation that tumors from 5 patients with GIST harbored mutations in the c-kit proto-oncogene. The mutations, located in exon 11, resulted in a gain-of-function of the enzymatic activity of the KIT tyrosine kinase. The finding that a mutation in GIST activates a kinase to behave in an uncontrolled manner was reminiscent of the mechanism of BCR-ABL in CML. It was hypothesized that activation of KIT functioned as a critical step in the pathogenesis of GIST. The corollary hypothesis, therefore, would be that inhibition of KIT could perhaps be an important new therapeutic strategy in this otherwise untreatable malignancy. Concurrent to these findings, it was determined that STI-571 is an inhibitor not completely specific for ABL or the kinase domain of the BCR-ABL fusion protein—STI-571 can also block the enzymatic activity associated with the transmembrane receptor tyrosine kinases KIT and PDGFR.[31,34-37] In particular, Heinrich et al[35,38] studied a mast cell leukemia cell line that harbored a mutation similar to that noted in GIST studies and demonstrated that STI-571 can inhibit kinase action of the mutant as well as the wild-type KIT protein. These observations were confirmed in GIST with preclinical modeling of human GIST cells by Tuveson et al,[37] who demonstrated that the inhibition of mutant KIT in GIST by STI-571 will lead to growth arrest and eventual apoptosis. These insights, coupled with the medical urgency to develop new therapies for metastatic GIST, set the stage for the rapid clinical development of STI-571 in GIST.

STI-571 for Metastatic GIST

The first patient with GIST began treatment with STI-571 in Finland in February 2000; the results have been reported by Joensuu et al.[39] The patient's tumor expressed KIT protein (by CD117 immunohistochemistry) and contained an exon 11 mutation in the c-kit gene. The patient had progressive, widely metastatic disease after failing extensive previous therapy, including multiple surgeries, chemotherapy, and even investigational antiangiogenic therapy. Within a few weeks of starting daily oral administration of STI-571, the patient exhibited a major objective clinical response that has been maintained for more than 18 months. The response detected by conventional magnetic resonance imaging was accompanied by a dramatic decrease in tumor activity detected by ^{18}FDG-positron emission tomography (PET) scanning. Serial tumor biopsies demonstrated that the tumor had been largely replaced by myxoid degeneration and fibrosis within 4 weeks.[39]

The encouraging results in the first patient, along with the elegance of the scientific rationale and the preclinical data, led to rapid expansion of this clinical translational research into large-scale studies of STI-571 in GIST. A multicenter Novartis-sponsored phase II clinical trial began in July 2000. Initially, 36 patients with unresectable or metastatic GIST were treated at the University Hospital of Helsinki, Dana Farber Cancer Institute, Oregon Health Sciences University, and Fox Chase Cancer Center. STI-571 demonstrated efficacy and minimal toxicity, with a partial response rate of approximately 60%. Although there were no complete responses, only 2 patients exhibited disease progression. Dramatic reductions in fluorodeoxyglucose uptake were observed on serial PET scans (Fig 3). In fact, PET changes have now been reported to occur even after a single dose of STI-571, indicating that rapid assessment and prediction of subsequent clinical response are possible with this functional imaging modality.[40]

This initial phase II trial was then expanded to 145 patients, and the preliminary results were presented at the plenary session of the American Society of Clinical Oncology (ASCO) meeting in May 2001.[6] Of 145 patients treated with STI-571 at a dose of 400 or 600

TABLE 2.   Response Rates After STI-571 Therapy in Patients With Metastatic GIST

Response	U.S.–Finland Collaborative GIST Study Group[6] (n = 86)			EORTC Soft Tissue and Bone Sarcoma Group[42] (n = 36)*
	400 mg/day	600 mg/day	Total	
Partial response (%)	50	68	59	69†
Stable disease (%)	27	24	26	19
Progression (%)	21	5	13	11

*Dose ranged from 400 to 1,000 mg/day.
†Includes partial or minor responses.

mg/day, 86 had follow-up exceeding 3 months and could be evaluated. The partial response rate was 59%, and only 13% of patients progressed (Table 2). There were no complete responses. Mutation in c-kit was found in 86% of the patients, and patients without mutation were less likely to respond. It is too early to determine the duration of response in patients with STI-571–sensitive GIST.

Confirmatory data have been reported from a separate study conducted by the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC).[41,42] In this study of 36 patients, presented by Van Oosterom at the same ASCO meeting in May 2001,[41] the rate of disease progression was only 11%, with 69% of patients demonstrating disease response (both major and minor responses) and 19% with stable disease. These remarkable results, summarized in Table 2, are fully concordant with the larger study of the U.S.–Finnish collaboration.[6] The results would be notable for any new agent in any disease and are particularly impressive for GIST, a disease that was essentially completely resistant to any systemic therapy before the advent of STI-571.

The preliminary trials of STI-571 in GIST were so successful that a group of sarcoma investigators gathered for a special meeting at the National Cancer In-
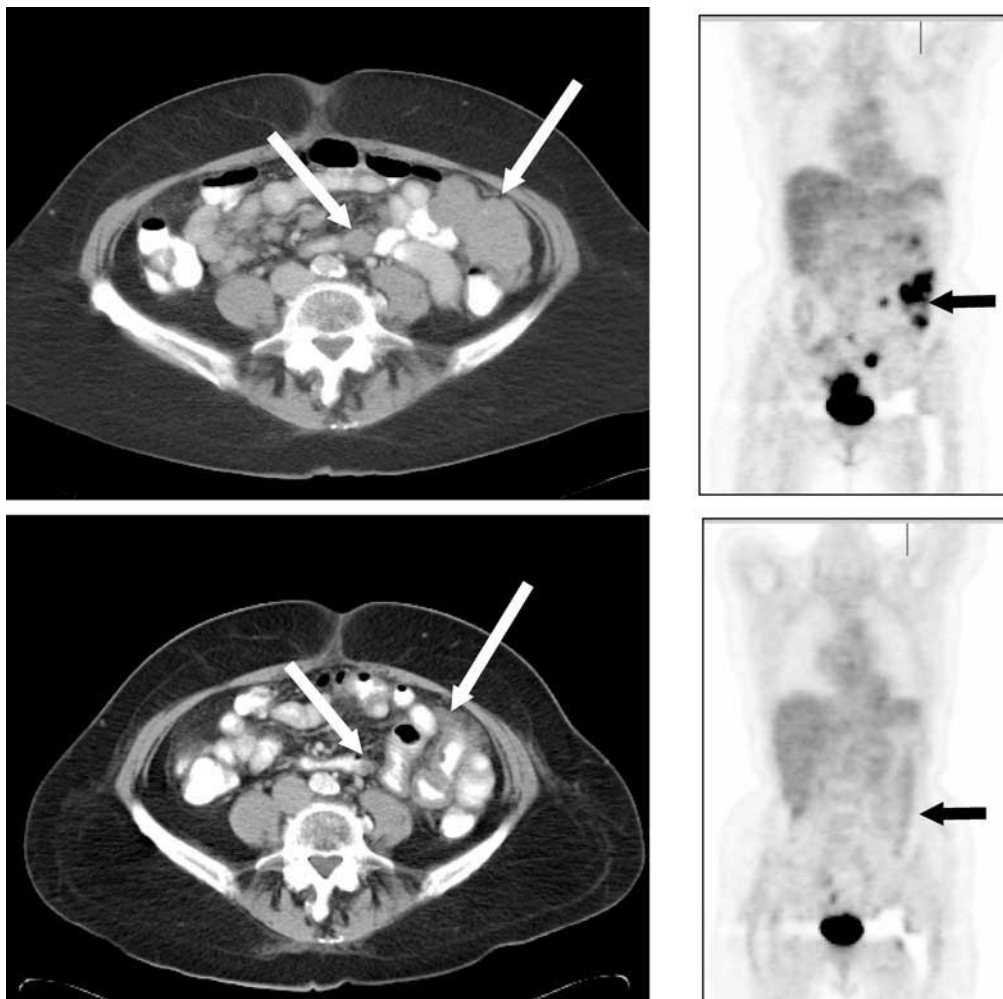

FIGURE 3. Clinical response to STI-571 in a patient with advanced, metastatic GIST. Response of a patient with intraperitoneal GIST before (top) and 3 months after (bottom) STI-571 therapy by CT (left) and PET scan (right). Notice that the tumor nearly disappeared by CT imaging and became "cold" on the PET scan after treatment. (Prepared with the assistance of Dr. Annick van den Abbeele and Dr. Milos Janicek, Dana-Farber Cancer Institute, Boston MA.)

stitute in November 2000 to discuss the results and design a study to expand access to this agent (not yet commercially available at that time) for GIST patients who might benefit from it. The result of this meeting was the rapid development and activation of North American Sarcoma Intergroup study S0033, which is designed to test whether high-dose STI-571 (800 mg/day orally given in divided doses of 400 mg twice a day) improves clinical outcomes compared with low dose STI-571 (400 mg orally given once a day). This trial is ongoing, but the study met full accrual goals (600 patients) and closed within 8 months of activation. A similar large-scale study currently being conducted in Europe and Australia under the auspices of the EORTC has similarly enjoyed very rapid accrual.

The optimal dose of STI-571 in GIST patients remains unknown and is the subject of active clinical trials. The first large-scale clinical studies of STI-571 in GIST were designed to assess secondarily the pharmacology and pharmacodynamics of STI-571 in GIST patients with KIT-positive tumors. The fact that this agent would be safe in this population of patients with extensive prior surgery in the abdomen also had to be established, because this was quite a different clinical scenario than the treatment of CML. Based on the preliminary data presented at ASCO, STI-571 is clearly safe and effective at doses similar to those used in the treatment of CML (400 to 800 mg/day orally).[6,40,41] The side effect profile in patients with GIST is also very favorable and similar to that reported in patients with CML. The major toxicities of STI-571 include mild fatigue, periorbital edema, diarrhea, and intermittent muscle cramping. The most medically severe side effects could actually come from excessive anticancer activity of the drug. Significant GI bleeding episodes have been reported in a few patients, postulated to be associated with massive tumor necrosis induced by this active agent.

Adjuvant STI-571 for Primary GIST

The role of adjuvant STI-571 is being evaluated because of its marked activity in metastatic disease, and because the risk of recurrence after resection of primary GIST is high and conventional chemotherapy is ineffective. STI-571 may possibly have its greatest impact on survival when there is minimal disease, as is the case after complete gross tumor resection when only residual microscopic disease may exist. The hypothesis is that STI-571 may avert or delay recurrence and thus prolong survival. The American College of Surgeons Oncology Group (ACOSOG) is leading a phase II trial sponsored by the Cancer Therapy Evaluation Program (CTEP) and Novartis to test the benefit of adjuvant STI-571 (400 mg/day for 1 year) in patients after complete resection of high-risk (10 cm tumor, tumor rupture, or multifocal tumors) primary GIST.[43] Comparison will be made to historical control data. A phase III trial led by ACOSOG is being finalized that will include patients with both high-risk and moderate-risk tumors (i.e., $\geq$ 3 cm). Patients will be randomized to receive

either placebo or STI-571 (400 mg/day for 1 year). A patient assigned to placebo will receive STI-571 therapy in the event of tumor recurrence. A preoperative ("neoadjuvant") phase II trial for primary GIST is being planned by the Radiation Therapy Oncology Group in collaboration with the American College of Radiology Imaging Network (ACRIN) imaging cooperative group. It will test the effectiveness of STI-571 as a neoadjuvant therapy in the preoperative management of patients with GIST. The advantage of these 3 trials is that tissue will be obtained before and after STI-571 therapy. Molecular analyses of the tissue specimens will be correlated with clinical responses or development of recurrence and, in the case of the neoadjuvant trial, the observed changes on serial PET scans.

Many questions apply to the use of STI-571 in the adjuvant setting. Certainly, the optimal doses or duration of administration have not been defined, which is why it is reasonable for physicians and patients to enroll patients in clinical research trials that will provide answers to these important questions. Nonetheless, as with other effective anticancer therapies, such as combination chemotherapy in the treatment of osteogenic sarcoma, it is likely that adjuvant therapy with STI-571 will improve outcomes if applied early in the course of GIST. Physicians should be encouraged to stay alert for available clinical trials for which their patients with GIST might be eligible.

CORRELATIVE STUDIES

The advent of STI-571 has revolutionized the clinical management of patients with primary and metastatic GIST, but our understanding of the genetic aberrations in GIST is just beginning to evolve. The 2 fundamental correlative questions regarding STI-571 use are (1) whether the type of c-kit mutation predicts sensitivity to STI571 and (2) what biologic mechanisms mediate tumor resistance to the agent

c-kit Mutation

The mutation in c-kit is usually somatic, although families with a germline mutation have been identified.[3,44] The reported percentage of GISTs that contain a c-kit mutation has varied. Lasota et al[45] reported that mutations in exon 11 of c-kit occur preferentially in malignant versus benign GIST and do not occur in leiomyomas or leiomyosarcomas. In the 2 largest GIST series, an exon 11 mutation was found in 71 (57%) of 124 cases and in 103 (52%) of 200 cases.[46,47] Recently, the c-kit mutation rate was purported to exceed 85% when the analysis included exons 9 and 13.[5,6] Methodologic differences among these retrospective studies might account for the variable prevalence of c-kit mutations. In addition, the type of tissue used for DNA extraction (archival paraffin material vs. frozen tissue) may affect the sensitivity of mutation detection. Moreover, patient referral patterns may vary among institutions. A more recent evaluation has shown that phos-

phorylation of KIT (and thus presumably, constitutive activation) is a universal finding in GIST regardless of whether mutations are present in the c-kit proto-oncogene itself.[48]

The presence of a c-kit mutation has been correlated with survival.[49] In a study from Japan involving a retrospective analysis of 124 patients with primary GIST with a median follow-up of 3.3 years, the 5-year disease-specific survival was 86% in 53 patients without a detectable c-kit exon 11 mutation, compared to 49% in 71 patients with a mutation ($P = 0.0001$).[46] Tumors with an exon 11 mutation were larger and more often invaded adjacent tissues. The patients with mutation-positive GIST had more frequent recurrences. However, a confounding factor is that 11 patients with metastases were included in the survival analysis. Also, the mutation rate of 57% may be inaccurately low; only exon 11 was examined in the study. In fact, 47 patients who were KIT-positive by immunohistochemistry did not have an identifiable mutation. Thus, whether c-kit mutation alone (in the absence of STI-571 therapy) actually predicts clinical outcome is unresolved.

Chromosomal Abnormalities

GIST has been shown to have several chromosomal abnormalities. In a study of 95 patients with GIST followed for 6 to 209 months (mean, 41 months), comparative genomic hybridization was used to screen for DNA copy number changes.[50] Benign GIST contained significantly fewer DNA copy number changes (mean, 2.6 aberrations per tumor) than malignant primary GIST (mean, 7.5) or metastatic GIST (mean, 9) (P <0.01). Moreover, benign tumors almost exclusively contained losses rather than gains. Gains and high-level amplifications at 5p and 20q and losses in 9p were seen only in malignant primary and metastatic GIST, and were more frequent in the latter. Gains and high-level amplifications at 8q and 17q were present more often in metastatic GIST than in benign or malignant primary GIST. The losses in 13q were less frequent in benign GIST than in malignant primary and metastatic GIST. Therefore, the increased numbers of DNA copy number changes and/or increased number of gains correlate with malignant behavior. These data suggest that, in addition to histopathology, immunophenotyping, and c-kit mutational analysis, other genetic changes may be used as complementary diagnostic tools and to predict the clinical behavior of GIST.

GIST Biology

As noted earlier, the similarity between the uncontrolled kinase activity of BCR-ABL in CML and the KIT molecule in GIST is striking. However, the identification of BCR-ABL as an important factor in CML was made more than a decade ago, whereas the identification of KIT as a critical pathogenetic factor in GIST has been recognized only within the past 3 years. Careful exploration of the variations in GIST from different patients may yield important new knowledge about the signal transduction pathways of GIST mediated through KIT. Such molecular analyses are under active investigation in the laboratories of Michael Heinrich and colleagues at the Oregon Cancer Institute and Jonathan Fletcher and colleagues at the Dana-Farber/Harvard Cancer Center. The manner in which different c-kit mutations affect KIT protein activity will be an important model for the structural biology of tyrosine kinases in general. The different sites of activating mutations may give rise to gain-of-function KIT mutants through various mechanisms, which could have important implications for the action of a kinase inhibitor such as STI-571. Such studies could also provide insight into the mechanisms of resistance and to the structure-directed development of new generations of selective kinase inhibitors. Finally, as has been shown in CML, the analysis of tumor specimens derived from patients whose tumors proved resistant to STI-571 may well indicate that several mechanisms of resistance are possible. In CML, for example, resistance to STI-571 in patients with advanced blast crisis has been associated with BCR-ABL gene amplification, as well as with the development of novel mutations in the kinase domain that presumably diminish the ability of STI-571 to bind to the ATP-binding site.[51-54] Knowledge of these mechanisms of STI-571 resistance will facilitate the development of new drugs and possibly avert resistance in the first place.

CURRENT USE OF STI-571 AND FUTURE CONSIDERATIONS

STI-571 has quickly become the first-line agent for metastatic GIST. Patients who respond may become candidates for surgical resection. Patients with stable disease may remain on the agent until disease progression becomes evident. Patients who become refractory to STI-571 are eligible for more traditional palliative therapy, such as hepatic artery embolization, radiation, or surgical debulking and/or intraperitoneal chemotherapy. The combination of STI-571 and conventional therapeutic modalities may prove to be the most effective approach for recurrent disease. Surgery remains the principle treatment for primary disease, but its outcome may be improved by neoadjuvant or adjuvant STI-571. The use of STI-571 for treating GIST will be tailored by the final results of neoadjuvant, adjuvant, and metastatic clinical trials and their associated correlative studies.

Clearly, the identification of STI-571 as an agent to target the critical pathogenetic mechanisms of CML and GIST represents a major advance in the treatment of these diseases. The information gained from these successes will have major implications for strategic drug development and for cancer biology in general. However, it is important to be circumspect and recognize that many challenges lie ahead in the management of GIST as well as in the extrapolation of these strategies to other human cancers.

First, it appears that very few GIST patients with

far-advanced disease exhibit complete responses to STI-571 therapy. It is possible that these responses may evolve slowly with chronic exposure to the drug; however, it is also possible that a subset of GIST cells will simply remain dormant under the influence of the drug without undergoing apoptosis. The challenge of future research will be to understand these different responses to STI-571 and to explain why certain tumor cells die while others remain viable. The molecular correlative studies in the current GIST trials should shed much light on these important topics.

Second, it will be critical to design new therapies for the GIST patients who are resistant to STI-571, either the small subset who are primarily resistant or those who acquire resistance after several months of drug administration. These patients have an important unmet medical need, and at the same time this clinical scenario provides a key scientific opportunity to study mechanisms of drug resistance and develop techniques to overcome those resistance mechanisms in vivo. Very rarely in clinical medicine is such an opportunity so clearly presented.

It will be important to use these experiences and extrapolate them to other human tumors through rational studies of molecularly targeted agents. At this point, it seems clear that the expression of KIT on human tumors is rather limited. More importantly, simple expression of a target such as KIT, in the absence of aberrant activation, does not necessarily mean that the target is pathogenetically critical to the cancer. Therefore, inhibiting the target may not have any clinical benefits if the target is only expressed but not activated, or expressed and not signaling. Only through careful molecular screening of tumors and rational application of biological principles will further progress in this area be made.

Because STI-571 also inhibits PDGFR, it offers a unique opportunity to study diseases in which STI-571 might be crucial to the pathogenesis of human tumors. Data already suggest that STI-571–mediated inhibition of the abnormally activated translocated PDGFR that characterizes dermatofibrosarcoma protuberans may be therapeutic.[55] An ongoing clinical trial is testing this hypothesis via an international collaboration in Boston, Oregon, Belgium, the Netherlands, and elsewhere.

Finally, it will be important to not be overly enthusiastic about the successes of STI-571 in treating CML and GIST. These 2 diseases appear to have relatively homogeneous pathogenetic mechanisms, each driven by a single dominant stimulus (i.e., aberrant signaling through BCR-ABL in CML and similarly uncontrolled signaling through KIT in GIST). Other common human malignancies, such as carcinomas of the breast, lung, colon, and prostate, appear to be the end result of multistep carcinogenesis. The abnormalities critical to the pathogenesis of common human carcinomas are still being identified. For example, genetic predispositions (such as mutations in the tumor-suppressor gene in familial polyposis) are clearly an important factor. However, the fact remains that most human carcinomas represent a complex calculus of multiple vectors, rather than the product of a single dominant factor as are GIST and CML. Thus many pathogenetic pathways may lead to the same histologic type of cancer. Nonetheless, the understanding of many individually distinct pathways likely will lead to important progress in treating even the most complex human malignancies. Only by starting with logical hypotheses, moving forward rationally in a logical, stepwise manner, and extrapolating from simple disease models to complex pathogenetic systems can the problems of cancer be solved. The exciting results of using STI-571 in GIST and CML indicate that effective therapies can be developed by the application of sound scientific principles to human diseases.

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